DRY MOUTH AND DRY EYES: COULD IT BE SJÖGREN'S SYNDROME?

Dr. Stanley Pillemer

DR. PILLEMER: Welcome to the National Institutes of Health. I am going to go over the topic today, "Dry Mouth and Dry Eyes: Could it be Sjögren's Syndrome?"

Probably most people will think, "Well, what is Sjögren's Syndrome? I've never heard of it." And when you look at those letters of the words it is kind of daunting because it is hard to figure out how to pronounce it. It is pronounced "Show-grins."

Now what is Sjögren's Syndrome? It is a disorder of the immune system, an autoimmune disease. What does autoimmune mean? It means that your immune system attacks yourself. The immune cells attack the other cells of your body. And you will have potentially systemic manifestations, which means it can affect many systems across the body and not just the eyes and the mouth as the title of my talk would have suggested.

Sjögren's Syndrome is also classified into what are called primary and secondary forms. The secondary type is when you have rheumatoid arthritis or some other autoimmune disease associated with Sjögren's Syndrome. Otherwise it is called primary.

And the main symptoms that usually bring a person to their primary doctor, dentist, or perhaps eye specialist are the dry eyes and dry mouth, and that is usually when the diagnosis is considered.

There are varying figures for the frequency of Sjögren's Syndrome because there are no definitive studies in populations to give us a very good idea of how many people are affected. It is thought to affect at least one million Americans, and there may be about four or so new cases per 100,000 population per year. Once you get the disorder, it tends to remain.

Henrik Sjögren, who was a Swedish rheumatologist, wrote a monograph on this syndrome, which is named after him, as part of his thesis in 1933. He thought about .05 percent of the population was affected with the disorder. And later on other studies suggested that it may be as high as 4.8 percent.

This is a disorder that predominantly affects women (nine to one).

Now you could ask yourself which of the following is true for you:

A) I have had a daily feeling of dry mouth for more than three months.

B) I have had recurrently or persistently swollen salivary glands as an adult.

C) I frequently drink liquids to aid in swallowing dry food.

Or it may be that D) More than one of these is true.

If you answered to yourself E) None of the above, this suggests that you do not really have the kind of dry mouth that you would experience in Sjögren's Syndrome.

I think anybody can see there is dryness in this picture of the mouth of a Sjögren's patient. Unfortunately, Sjögren's usually comes to a person's attention because they are going to the dentist more often. They are starting to have a lot of cavities and often, after about eight to twelve years, the diagnosis tends to be made. So it is not obvious in the beginning.

This also reminds me of the different approaches. I am a rheumatologist, but I work in the Dental Institute and, of course, in the Dental Institute the prime interest is in the dry mouth symptoms, although we look at this as a systemic disease. And when you look at different institutes, of course people have different interests. I remember walking into the Office of the Clinical Director of the Mental Health Institute, and he had a big sign up there which said, "Just because you are paranoid does not mean it is not true."And he also had another sign which said, "The beatings will continue until morale improves," which I think is sort of playing with the mind a little bit. Whereas, in the Dental Institute the Clinical Director, who used to run the Sjögren's Syndrome Clinic, had a sign up there, which said, "Spit Happens."

Now in this case you can see what happens when spit does not happen. One of the things that happens when spit does not happen is unusual dental cavities. At the gum line there are unusual erosions of the teeth or cavities. The cutting edge of the teeth may also have striking abnormalities.

Now if your mouth stays dry over a long period of time, you can develop other complications such as fungal infections. You can see at the junction of the upper and lower lip (at the corner of the mouth) there are a couple of little scabs, little injuries there. This tends to be associated with fungal infections and it is called angular cheilitis. To prevent it you can either put Vaseline there, or you can use an anti-fungal ointment to improve the angular cheilitis while you treat the fungal infection in the mouth.

Now why would somebody have dry mouth? It is often incorrectly blamed on age because the most common cause is medications. For example, antihistamines will give you dry mouth, as will blood pressure pills, antidepressants, and a number of other medications. About 400 different medications can give you dry mouth. Of course, there are many that do not.

I just had a patient on Thursday who had quite a few problems. She turned out to have Sjögren's Syndrome, but she was also on medications for irritable bowel syndrome, an antidepressant, and four other medications that would cause dry mouth. So it happens

not only to people without Sjögren's, but Sjögren's patients may aggravate their situation by being on these medications.

Now there you can see the salivary glands; the parotid gland is the one under the ear. There is one under the tongue called the sublingual gland. And there is one which would be at the angle of the jaw, which is the submandibular gland. These produce the saliva. In Sjögren's Syndrome they can become swollen. So if you have already had mumps and you start to get it again, it means there is some other problem. It is not mumps, because you should only get mumps once.

Recurrent swollen salivary glands can be associated with many disorders and have different causes. Diabetics may get a swollen gland. You may have an obstruction of the duct where the saliva comes out into the mouth and it swells every time you eat something, and afterwards it goes down.

You can see on the left the gland looks different -- this is a microscopic slide -- than it does on the right. What has happened on the right is that all these cells of the immune system have come in and are creating an inflammatory response.

The salivary glands, in essence, are something like a bunch of grapes. You have the acini, which are like the grapes, and then you have various ducts (like stalks) that go out and drain into the mouth. These acini, or grapes, are hollow spherical structures which are lined by cells, called epithelial cells. And it is these cells that make the saliva. I have x'd out some of them. This is what happens when you lose functional units because the medications are interfering with their function, for example, or because you have actually lost them.

Now, why else might you lose them? One of the most profound reasons for losing the salivary glands is having a head and neck tumor and having radiation. Direct radiation produces rapid changes. A less obvious cause is when you have had thyroid problems in the past, and the thyroid is treated with radioactive iodine. The radioactive iodine can damage not only the thyroid gland to get rid of the tumor, but it also affects the salivary glands, and years later you may end up with decreased secretions.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: Well, Synthroid will replace what is missing from the thyroid gland but it does not help you with your salivary or tear glands.

Why do we get Sjögren's syndrome? Well, we know that a number of viruses attack the salivary glands and the tear glands, et cetera. When a virus is seen by the body, immune cells will attack it. A virus can reside in cells sometimes, so if you attack the

virus in a cell you may damage these units (cells), and you may lose some function because of that. Although many viruses have been suspected as having a role in Sjögren's syndrome, none of them has been proven to cause the disorder.

In Sjögren's syndrome, how do the immune cells attack? They produce antibodies. These Y-shaped antibody molecules could block the substances produced by the nerves, i.e. acetylcholine. The acetylcholine binds to the epithelial cells and stimulates them to produce their secretions.

Receptors in the salivary glands and tear glands and other glands that produce secretions across the internal and external lining surfaces of the body can be blocked. The antibody binds to the muscarinic receptor. There are different types of muscarinic receptors called M1, M2, and M3. The M3 receptor is the important one in the salivary glands that the acetylcholine sticks on to like a key going into a lock. And if you block the key from going into the lock you might decrease secretions.

Now there is also another category of chemicals called cytokines, and these cytokines are made by immune cells. Lymphocytes are the examples here, but there are other cells of the immune system as well. A lymphocyte is a type of white blood cell and these substances, such as cytokines, may interfere in some way with the binding of the acetylcholine, or may affect the machinery of the cell so that saliva production is decreased.

The actual mechanisms for this have not really been unraveled yet, but theoretically, this is one of the possibilities.

And there are actually drugs that have been developed now to stimulate the M3 receptor, replace the activity of the nerves, and stimulate the salivary glands to work harder. An example of this is a drug called pilocarpine. It is also known as Salagen. Pilocarpine binds to those receptors and makes the glands work extra hard, even though they are damaged, to produce a little more saliva or tears and improve surface moisture.

Now I mentioned that Sjögren's syndrome can occur in a secondary form, where it is associated with diseases like rheumatoid arthritis. In Sjögren's itself you can have arthritis, but this arthritis is not generally considered to be rheumatoid arthritis. It is milder and does not generally cause deformities. It responds very well to the standard treatments that would be used for rheumatoid arthritis. It just melts away. Whereas, rheumatoid arthritis tends to be more refractory.

There are a number of other diseases, for example scleroderma, a disease where you get scarring of the tissues throughout the body, and the skin hardens. That is why they call it scleroderma. Sclero means to harden. And you can see the folds in the lips.

You can see that this patient actually has a very characteristic face, which they call mauskopf (mouse head). The same sort of appearance often occurs in patients who have scleroderma. So Sjögren's syndrome can be associated with a number of other disorders.

Now I am going to move on to the dry eyes aspect. Now, these questions actually come from the European criteria for Sjögren's syndrome. I have a questionnaire that asks this:

A) I have had daily persistent troublesome dry eyes for more than three months.

B) I have a recurrent sensation of sand or gravel in the eyes.

C) I use tear substitutes more than three times a day.

Now, if more than one of these is true for you then you have the level of dry eyes that requires treatment, and that would be consistent with Sjögren's syndrome.

If you said none of the above then dry eyes is not a significant problem for you.

Now this [pointing to a slide] is just to show one of the tests. This is not somebody who has really got very bloodshot eyes from overdoing things. This redness of the surface of the eye is caused by a red dye called rose bengal. We do not use rose bengal so much anymore because it does irritate the eyes, too. But what it does show is that the surface of the eye is damaged. The dye will stick to the damaged cells on the surface. Lack of moisture results in damage to the surface of the eye.

You can also take a little rectangular filter strip, a little piece of blotting paper. You place one end in the eye and that will absorb the tears. You can measure the length of the movement of the tears. If it is less than five millimeters in five minutes, that is consistent with Sjögren's syndrome.

What could cause dry eyes? It could be that the nervous system is not working properly in stimulating the glands, but the most common cause is that you are just not producing enough tears.

The tears typically have three components. Right on the eyeball itself there is a mucus layer, then you have a layer of water, and then on the outside you have an oil film which holds the tears in place. The oil layer decreases evaporation. So tears, which seem like simple drops of salt water, are incredibly complex, as is saliva, and have many, many components.

In Sjögren's syndrome, the general problem is that the eyes are not producing enough of the water part of the tears, the aqueous part. In other dry eye conditions it may

be you are not producing enough oil. So there is excessive evaporation, and you can have what is called an evaporative tear loss.

Of course, anybody can have an evaporative tear loss, if you are out in a very strong wind, if it is really cold, or if the humidity is very low. So all of these dryness symptoms can be improved by protecting yourself and having less exposure to drying conditions. But nevertheless, in Sjögren's syndrome, you are not making enough water because the tear glands are not functioning properly.

So what can you do about it? Well, you can use artificial tears. You can use ointments that block the loss of tears, and in extreme cases, there are even glasses that you can wear, which have chambers that cover the eye completely like goggles, so that you do not lose moisture from the eye.

Our typical patient with Sjögren's syndrome is a woman in her 50's. She is a nonsmoker. She walks around with a water bottle in her hand. When she is evaluated, she is there taking sips of water all the time. She has her eye drops at the ready. She is putting in these eye drops frequently. She tells you that she is very tired, that fatigue is a very big problem in Sjögren's syndrome. And she makes frequent trips to the bathroom. There are a couple of reasons for this. One is that she is taking these frequent sips of water all day. She is drinking more than most people. And the other is that the kidney does not concentrate urine as well. So there is more of a tendency to put out more urine, because Sjögren's syndrome can affect the kidneys, too.

I have had patients tell me, "I gave up my job. I had to retire early." For example, a teacher said, "I could not speak, my mouth was so dry. I could not speak all day to the students."

People with dry mouth have difficulty chewing and swallowing. The saliva helps to move food around in your mouth when you are chewing it. It helps you to swallow it. Without saliva, people may develop malnutrition. They may lose weight. They may tell you the food does not taste good anymore. Often they change their diet. They do not have to, but it is very, very uncomfortable, and it is just a natural course of events.

Sjögren's syndrome patients go to bed early. Sometimes because they are just so tired, but another reason that you hear less often is that their eyes are burning so much. They have been putting in eye drops all day. The only thing they can do now is just close their eyes. Once they close their eyes, they may as well go to sleep, because it is night time.

And I have had patients tell me that they do not like to drive on the highways because their eyes are burning so badly that they have to keep stopping. So it is very

unpleasant to drive longer distances.

So, Sjögren's syndrome does have a major impact on quality of life.

I have mentioned some of the things that you can do if you have lost these cells in the glands that produce the secretions. You can stimulate the secretions by, for example, sugar free candy or chewing gum. It is very important that it is sugar free because if you have sugar in things that you are chewing, eventually your teeth are going to pay a toll, and if you have dry mouth you are at even more risk than the general public for that.

Electrical stimulation. Well, there is one device, but it is not used very much, but it stimulates the production of saliva.

Pilocarpine I mentioned to you. And now there is a new drug called cevimeline, which is a new M3 receptor stimulator, and it has recently come on to the market as a drug known as Evoxac.

And you can replace the missing fluids, which we have mentioned, with not only sips of water. You can use artificial saliva, but it is not very well tolerated by most people. They take it for a little while, and they say it does not taste good. It did not help that much and they would rather just sip water. They do not like the texture and so forth.

So how do you diagnose Sjögren's syndrome? Well, part of it is 1) the dry eyes symptoms; 2) the oral symptoms of dryness; 3) evidence of keratoconjunctivitis sicca (KCS), which is inflammation of the eye. The presence of KCS is demonstrated by the filter paper test called the Schirmer's test that I told you about, or by a dye test like the rose bengal test, where the ophthalmologist will look through a slit lamp to see whether the dye is taken up. It can even be scored to give you an idea of how bad it is.

And 4) there is the presence of focal sialadenitis, which simply means inflammation of the salivary glands. This involves taking a biopsy from the inside of the lips, and it is looked at by the pathologist to see how many of those cells, called lymphocytes, are present. The biopsy is scored according to number of lymphocytes which reflects how bad the inflammation is.

Another category of diagnosis is 5) other evidence of salivary disorder, including decreased saliva production as well as scintigraphy and sialography. There are many ways of collecting saliva, but essentially you can collect it individually from the glands or you can collect whole saliva. If the flow is low below a certain point, that would meet one of the criteria for Sjögren's syndrome.

Scintigraphy is used to look at the uptake of radioactive material in the salivary glands because the techicium pertechnetate, which is the substance used, follows the

secretions in the glands. If you are not producing secretions, it will show up on the scintigraphic scan.

In sialography, you can take a dye and put it into a duct in the mouth, to show that there is an abnormal pattern. Then 6) there are the autoantibodies. These are Y-shaped antibody molecules, which are directed against cells or other molecules in your body. One of the prominent ones for Sjögren's syndrome is anti-SSA, and another one is anti-SSB. So if you have either of those and if you meet four of six of these criteria, we would say that you have Sjögren's syndrome.

The exact balance and how stringent you have to be with these components to make the diagnosis has varied because there are Greek criteria, there are Copenhagen criteria, et cetera. Several centers have come up with their own criteria in a European consortium. We are working with them now to try to develop a final international agreement on the optimal criteria for diagnosing the disease.

Sjögren's syndrome does affect multiple systems. People may have dry cough, dry skin, and other problems associated with the disease. It also could have long-term complications like lymphoma, which is a tumor of the white blood cells, which affects the lymph glands. Lymphoma has a 44-fold increase in Sjögren's syndrome, compared with the general population.

So how do we treat all of these problems?

The important thing here is we can attack the immune cells in Sjögren's that are causing the problems and we can interfere with the molecules, called cytokines, that are produced by the cells. And we are doing some studies with etanercept, where we block the cytokines. This is blocking one of the factors that stimulates the inflammatory response, which is produced by the cells of the immune system.

We are also doing a study on thalidomide, which also is something that is good in decreasing inflammation, and another study on DHEA, which is one of the steroid hormones, which has a mild male hormone effect because most individuals affected with Sjögren's are women and there seems to be a hormonal component. There is evidence that male hormones may decrease the intensity of Sjögren's syndrome.

So I will stop there. If you have any questions I welcome them and thank you very much.

(Applause.)

DR. PILLEMER: And today we also have Dr. Vidya Sankar here from the clinic who is a dentist, who can answer a lot of dental questions. Would you like to come

down? We also have Joan Manny, a nurse, who volunteers at the clinic, and Roseanne Leakan, our Research Nurse.

[A question from the audience]: Yes. I have glaucoma and I take pilocarpine and I have taken it for 20 or 30 years. Glaucoma runs in my family. And about a year ago my eye doctor, who is an ophthalmologist, told me that I have dry eyes and to use tears, you know, that you buy. I was wondering, you mentioned pilocarpine as sort of a therapy for dry eyes. Is that true?

DR. PILLEMER: That is true. When you take it in tablet form it not only helps dry eyes, but it helps dry mouth, and it was approved actually in Sjögren's syndrome mainly for the dry mouth -- the help it gives to dry mouth -- but it does increase secretions throughout the body, including sweating.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: The eye drops will only have a local effect on the eyes; not much gets into the body. When you take the eye drops you should be careful if you are taking it for dry eyes over the long term; you should get the kind that comes in separate little dispensers and not in a big bottle. The ones that are in a larger container usually have preservative in them, and the preservative will irritate your eyes, and you may become allergic to it. And it actually damages the eye cells, on the surface.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: Many people wake up at night with dry mouth and one of the problems is mouth breathing, especially if you lie on your back. Usually, once you wake up, if you drink something or you wait a little while, the saliva will moisten your mouth and then you are okay. That is not the sort of dry mouth that you have with Sjögren's syndrome, but perhaps you should change the position that you sleep in, or consider whether you might have sleep apnea.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: One of the things that happens is that when the tear film is inadequate and the eyes are dry, vision becomes a little fuzzy. And you will also have other problems, including sensitivity to light.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: When you say exercise, what kind of exercise? I would say it would not do any harm but there are no studies that have really looked at that.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: There are many causes of dry eyes so it could be from medications that your eyes are relatively dry already. It could be that you have keratoconjunctivitis sicca, where you have the immune process, but it is confined to the eyes and may occur in the absence of Sjögren's syndrome. There are topical treatments, such as eye drops, that you can take for that.

But if it is mild, what you are talking about is evaporative loss so when there is air conditioning or circulating air in the room, or you are in a car and the air conditioning is on blowing in your eyes, it rapidly bothers you. You may find that in winter when you go out, you come back and your eyes are gritty for hours. And the way to deal with that really is to use these eye drops, and again the ones without preservatives if you are going to do it long-term.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: Artificial saliva derived from cellulose. When cellulose-type molecules are suspended in liquid, they hold moisture quite well. The same compounds are used in the eyes. It seems that the mouth gets very sticky as soon as it is dried out, when you use the artificial saliva.

It is sprayed into the mouth, and most people do not use it for more than a couple of weeks. I think there was one patient I came across recently in the clinic who uses it regularly, but I do not think it helps as much as sipping fluids or pilocarpine or cevimeline, these new drugs that stimulate the secretions.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: Well, yes, these are all Sjögren's type problems. Although I must say that there has been a bit of controversy about the thyroid, whether or not hypothyroidism and underactive thyroid is related. Epidemiological studies in this area suggest that it is the age group. It is the same age group that gets Sjögren's and gets hypothyroidism.

But certainly a lot of our patients have thyroid problems. Having the dry eyes to the point where you have to have punctal plugs. First, they may put in what they call collagen plugs into the tear ducts, because the tear ducts drain out all the tears, and the tears actually go into the nose.

There are a couple of types of plugs. They have a collagen plug which just stays for a little while, and a silicon plug, which they can take out. Then as a final resort they can cauterize or use laser to seal the ducts. Usually, the ophthalmologists insert the plugs first to test that you are going to benefit, because if it is not severe enough, for example,

and you sealed off those ducts, then you can end up with somebody who is producing tears constantly and they are running down their cheeks.

Has that answered your question? Those symptoms all fit with Sjögren's syndrome.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: If she is on medications like pilocarpine or cevimeline, that may help in some cases. If you do not have enough gland tissue or if the immune response is blocking it so well that even these drugs do not help, then obviously that does not solve the problem.

Now as to prednisone or other steroids, everyone thought they would be useful. I am a rheumatologist, and rheumatologists hand out steroids like candy. If you have got inflammation, steroids are good. But it does not seem that in the one study that really was randomized, double blind and placebo (fake medication) controlled, that it was beneficial to use prednisone.

People with Sjögren's syndrome who have chronic swollen glands, (parotid glands, submandibular glands, or lymph glands), they will tend to be treated with steroids.

Methotrexate was looked at in a study in Greece and it seemed to be beneficial, but it was not a controlled study. It did seem to help people with chronic cough. The lining of the lung is dry in Sjögren's syndrome, so you have a dry chronic cough from that, and that seemed to get better. So those treatments are not unreasonable in principle.

Another one which we think is probably quite helpful is Plaquenil, which is a drug used in a number of diseases like rheumatoid arthritis and systemic lupus. It seems that the labs get better and stay better over a long period of time. We do not have any peer-reviewed information on that yet, but in a study that we did, we found that patients improved their saliva, not the eyes, for those who were on the placebo, their salivary flow got worse.

So I think it may be worth a try anyway if she is on these other drugs like methotrexate. You do not have to go off methotrexate, if it is giving some benefit. You can add Plaquenil, otherwise known as hydroxychloroquine, an anti-malarial drug.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: Well, if your question is whether Sjögren's patients get canker sores, then yes, they do. But canker sores are very common in the population. It is one of the commonest sores with our without dry mouth.

But if you have dry mouth for a long period of time, you are not only likely to develop problems with fungal infections that I showed you, but you are more prone to trauma, because your tongue cannot move around as easily in the mouth. When you are chewing, it is easier for your cheeks to get cut, et cetera. So you are more likely to get sores in your mouth, and Sjögren's patients do get more sores.

Is that your question?

(Inaudible—Someone not at a microphone speaks.)

DR. SANKAR: *(Not at microphone.) (Inaudible)* -- if it is a certain type of sore that develops, you may be able to take preparations beforehand to reduce the length of time that you have the sores in your mouth. If you get them in all different areas of your mouth, you may decrease the number of areas that are affected, but there is no preventive medication that I know of that works 100 percent.

DR. PILLEMER: And what do you recommend for those sores, in general?

DR. SANKAR: Well, it would depend on what type of sore it is. Some people say they have cold sores or canker sores and they may fall into a number of different categories. It might be like stress ulcers or it could be viral. It could be due to a virus or it could be an overgrowth of fungi, and they may all look similar to you when you open your mouth and check it out in the bathroom mirror, but they are caused by different things. There is no one medication that I could recommend to you without seeing it first, diagnosing it, and then offering a remedy after the fact.

DR. PILLEMER: Also, I just want to point out to you that Dr. Sankar belongs to that category of dentists called oral medicine specialists.

DR. PILLEMER: Dentistry is really a specialty of medicine, and in oral medicine they spend a lot of time on these lesions or diseases of the mouth and face.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: I do not think halitosis is specifically an effect. Well, I will ask Dr. Sankar this.

DR. SANKAR: Because of the dryness you may not be able to cleanse your mouth as well, and the increased debris in your mouth may lead to a halitosis problem. Advanced periodontal disease may contribute to a halitosis problem and that might be linked to the dryness as well. But Sjögren's itself will not make you develop halitosis.

(Inaudible—Someone not at a microphone asks a question.)

DR. SANKAR: Because of the dryness, a lot of patients develop a very, very sensitive tongue. They get a burning sensation sometimes. And that could be due to the dryness itself or it could be due to an overgrowth of the fungus in their mouth. And stimulating saliva may help that. It may have to be treated with antifungals for a short period of time, but we do have a good number of patients who do have the dryness and the burning as well.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: Raynaud's phenomenon occurs in a number of different rheumatic diseases, rheumatoid arthritis, lupus, et cetera. So it is not specific, but it is fairly common in Sjögren's syndrome. Now what is Raynaud's phenomenon? We can all identify with it; we go out in the cold and we blanch a little bit. Our blood flow is decreased into our hands, let's say. And your hands may go a little bit blue eventually with cold and then when you go back inside, you find that your hands become very red, and then you go back to normal.

Now that could happen normally but the Raynaud's phenomenon is an extreme. You are blanching, and very often, it is well demarcated. You find yourself with a couple of fingers for which you can draw a line exactly where the Raynaud's ends. You get very, very pale. You experience pain because there is so little circulation going in.

And if it continues or if it is very extreme and you do not take precautions, you can end up with problems. At the first level you may get a little bit of gangrene, which you would not think of as gangrene. It is really in the pulp of the fingers. So you will see a little dent there and it will be kind of itchy and there will be an area where the skin kind of scales up. So you see little scaly points on the fingers.

If it goes even further, and you have severe problems, you can actually have gangrene and lose fingers and toes from what would be regarded as a normal exposure. Something that would not bother somebody else. You have gone out, you were wearing your gloves and boots, and the whole thing, but you had developed that problem.

It is not a very good marker, but certainly on the order of 30 to 50 percent of Sjögren's patients have Raynaud's. And when it is severe -- and it is severe in a minority of the patients who have Raynaud's with their Sjögren's -- then you would usually give calcium blockers like nifedipine as a treatment.

And also, of course, you have to keep your whole body warm, because it turns out that although it is most extreme in the digits, Raynaud's is a total body phenomenon, and there have been studies that show, for example, that even the circulation in your lungs is decreased. So it is important to cover yourself up, to avoid extreme exposure and, if

necessary, to take medications to improve your circulation.

We wanted to do the study because DHEA, dehydroepiandrosterone as it is otherwise known, is a weak male hormone. So part of the problem is it can cause acne, and we have had some patients in our study who developed acne while they were taking it, but it turned out that really they had had acne before, for which they had been followed by a dermatologist. In adult acne, you get lesions that are less prominent on your face and more often on the trunk.

The other problem you can get theoretically is that you might start to look a bit like me. You might lose some hair on top. You may develop a beard, et cetera. Body hair in the wrong places. In actual fact, we have not seen that. We use a fairly good dose. We use a dose more than they recommend in the health food stores.

So the question of the health food stores is, should you use that? Well, you know, we are doing a study here so it must be good, let's do it. I would say no. And the reason why I would say no is the Arthritis Foundation has a newsletter, and they sent out to try and see how good these products are. They got a whole bunch of DHEA preparations and sent them out to the labs, and there were some that had such low DHEA in them.

So you do not know what you are getting, because it is not really something that the FDA has monitored when you buy it that way. So we were encouraged to do the study for that reason, to get an answer to whether you should use it or not.

We use a highly purified compound, which has been prepared by our pharmacy. It is not an FDA-approved drug.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: One of the first questions people ask us is whether Sjögren's Syndrome runs in families. It is a very good question, because there does seem to be an increased risk, but I think it is a minor risk. It seems that there is not sort of a Sjögren's gene that we know of yet. It is not one of these things that everybody is going to get. If both parents have Sjögren's, are you going to get Sjögren's? That would not be a foregone conclusion.

But there are certain genes associated with the immune system which seem to be overrepresented in people that have Sjögren's syndrome. So there are various genes that predispose you to it. If you have a family member with any autoimmune disease, you are probably at a slightly increased risk for developing an autoimmune disease yourself, including Sjögren's syndrome.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: In Sjögren's syndrome, the glands swell because there is an invasion of lymphocytes. You can sort of think of it as when you go into the city. All these cars get on the highway, and they cram up all the parking spaces everywhere. And there is traffic of lymphocytes, which are inflammatory cells of the immune system. And they go into the glands. They produce substances which fill the glandular tissue with more cells and more liquid.

I guess the difference is that the city does not get bigger to take up more space to allow more cars in, but that is what happens with the glands.

But on the other side, you can have a problem with swelling of the glands that is not related to the lymphocytes going in there, all these cells cramming in. You could have a blockage of a duct, for example. When that happens -- when you have something sweet or whatever -- and around meal time you will get swelling.It is usually on one side and not both, and it is uncomfortable and then it settles down.

When you have salivary gland swelling, what do you do about it? If it is in Sjögren's syndrome, you can use warm compresses. You can massage the gland. You can use guaifenesin, for example, which is something they put in cough mixtures to help you make more secretions that are less viscous, so you can clear them.

Another treatment that decreases the viscosity of the secretions is SSKI. It is a potassium iodide solution, which I guess would have to be prescribed.

(Inaudible—Someone not at a microphone asks a question.)

DR. PILLEMER: Well, excessive moisture in the eye can indicate that the tear ducts are blocked, for example, and tears accumulate, because they cannot drain out of the eye.

Another cause might be medications. Just like pilocarpine in one context, there are some medications that could increase tear production. It can also be just your natural tear production.

Another possibility also is allergies to various molds, et cetera. Your eyes will feel irritated. You will make more tears.

It can also happen if you have been outside, and it was very dry, that your eyes have become irritated in the outside environment. When you get in the car, your eyes will continue to have symptoms. That would be common after cold exposure. It would not be abnormal.

Any more questions? Well, if anyone has any more questions I would be happy to

answer them. Dr. Sankar would also be happy to answer questions. [PAUSE] Thanks very much for coming today.

(Applause.)

* * * * *